

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number:

0 004 040
A1

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 79100614.1

(22) Date of filing: 02.03.79

(51) Int. Cl.²: A 61 K 31/195

A 61 K 31/19, A 61 K 31/60

A 61 K 31/405

// (A61K31/195, 31/195),

(A61K31/195, 31/19), (A61K31/60,

31/195), (A61K31/60, 31/19),

(A61K31/405, 31/195),

(A61K31/405, 31/19)

(30) Priority: 03.03.78 US 882975
14.02.79 US 12043

(43) Date of publication of application:
19.09.79 Bulletin 79/19

(84) Designated contracting states:
BE CH DE FR GB IT NL SE

(71) Applicant: Merck Patent Gesellschaft mit beschränkter
Haftung
Frankfurter Strasse 250
D-6100 Darmstadt(DE)

(72) Inventor: Ehrenpreis, Seymour
4339 Birchwood Avenue
Skokie Illinois 60076(US)

(72) Inventor: Comaty, Joseph E.
1471 Brown Street
Des Plaines Illinois 60018(US)

(72) Inventor: Balagot, Reuben C.
4264 N. Hazel
Chicago Illinois 60613(US)

(54) Method of using inhibitors of breakdown of enkephalins and endorphins for effecting analgesia and for the production of pharmaceutical preparations and analgesics.

(57) A new class of analgesics is provided by substances that inhibit breakdown of endogenous substances such as enkephalins and/or endorphins. The analgesic effect of an enkephalin breakdown inhibitor is greatly enhanced by being combined with an antipyretic, anti-inflammatory analgesic, herein designated as an aspirin-type drug. Specifically, both D-phenylalanine and D-leucine, each an enkephalin breakdown inhibitor, when used separately provides excellent analgesia in animals and man without developing tolerance or addiction in either species. Use of a combination of D-phenylalanine and D-leucine provides a greatly enhanced analgesia approaching the analgesia achieved by morphine. Analgesia by the latter combination is very long-lasting in animals. The injection of a combination of D-phenylalanine and an aspirin-like drug that is antipyretic and anti-inflammatory, in an animal provides a greatly enhanced analgesia approaching the analgesia achieved by morphine. Analgesia by D-phenylalanine is very long-lasting in humans.

EP 0 004 040 A1

BEST AVAILABLE COPY

FIELD OF THE INVENTION

This invention relates to analgesia. More particularly, this invention relates to a treatment of animals and humans by the administering of a substance that inhibits
5 and/or delays the inherent breakdown of a class of naturally occurring analgesics that are created and exist within animals.

BACKGROUND OF THE INVENTION

Enkephalins and endorphins are morphine-like substances which have recently been discovered to be endogenous
10 in various animal species, including mammals and man. Enkephalins and endorphins are peptides and/or polypeptides. Enkephalins are normally present in the brain.

It has heretofore been observed that enkephalins and endorphins have an ability to act as analgesics, to abolish
15 pain, when administered to various animals by certain special routes (e.g. directly into the brain) that pose practical drawbacks to useful administration. These substances have a drawback that they are addicting, and tolerance develops to them. They have an additional drawback of having an effect
20 of very short duration of action, due to their rapid destruction by other substances endogenous to animal species, including mammals and man. These endogenous substances that destroy the action of enkephalins include at least two known enzymes, carboxypeptidase A and leucine aminopeptidase.

D-phenylalanine and DL-phenylalanine are known chemicals listed in the Merck Index.

Use of phenylalanine has been reported from the Faculty of Medicine, Buenos Aires, Argentina in "Therapy of Depression by Phenylalanine", Arzneim.Forsch, Vol. 25, NR1 (1975), and "Use of D-Phenylalanine In Parkinson's Disease, Arzneim.Forsch, Vol. 26, NR4 (1976). In the report on treatment of depression, DL-phenylalanine was administered in quantity of 50 or 100 mg. per day for 15 days, and D-phenylalanine was administered in quantity of 100 mg. per day for 15 days.

A commercial drug, sold under the Trademark "Deprenon", is available for treatment of depression, by oral ingestion of 3-4 capsules per day. Deprenon's specifications state that each capsule contains:

D-phenylalanine - 50 mg.

Mannitol - 90 mg.

Pervidone - 4 mg.

Magnesium Stearate-3 mg.

It is herein postulated that since enkephalins are endogenous, but after being formed and released for effecting endogenous analgesia, they are then rapidly destroyed by other endogenous substances, it might be possible to secure a longer lasting, or prolonged, endogenous analgesic effect if the said endogenous destruction of the endogenous analgesic substance can be inhibited and/or delayed.

10 One object of this invention is to provide a safe and practical method of securing in mammals a long lasting, or prolonged, endogenous analgesic effect from naturally occurring enkephalins and/or endorphins.

In testing certain substances to serve as inhibitors of the endogenous destruction of enkephalins, it has been discovered that by virtue of such actions, certain of such inhibitors operate by such a mechanism to abolish pain.

The substances discovered constitute an entirely new class of analgesics. The most potent substance tested thus far is D-phenylalanine. Another substance with a significant effect is hydrocinnamic acid. It is presently anticipated that leucyl valine may also prove to have a significant effect.

Another substance with a very significant effect is D-leucine. The combination of D-phenylalanine and D-leucine has proven to result in a potentiation of the analgesic activity of either substance used alone. The chronic administration of the combination of D-phenylalanine

and D-leucine has produced very long-lasting analgesia in mice. Each of the foregoing substances is available in a powder form and is water soluble.

DL-phenylalanine (a mixture of D-phenylalanine and L-phenylalanine) and DL-leucine (a mixture of D-leucine and L-leucine) may be economically used, respectively, as a source of D-phenylalanine and D-leucine whose utility is disclosed herein. The DL-form of those two chemicals is less expensive than the pure D-form of those two amino acids.

The analgesic characteristics of the new class of substances were determined by examining animal reaction to a single treatment, referred to as an "acute" experiment or test, and also to prolonged administration, referred to as a "chronic" experiment or test, to determine if tolerance develops.

It has also been postulated that the analgesic effect of the new class of substances might be enhanced or potentiated by combining the substance with an antipyretic, anti-inflammatory analgesic, which is commonly referred to as an aspirin-type drug. The theory in support of this postulate is that such aspirin-type drugs are known inhibitors of various enzymes, particularly prostaglandin synthetase. It has also been observed that aspirin-type drugs may enhance, or potentiate, the action of narcotic analgesics, and such drugs have been used in such combinations of ingredients as: codeine and aspirin, and Darvon and aspirin.

Thus, another object of this invention is to provide a new combination of analgesic materials in which

the analgesic effect of the substances of the combination will be greatly potentiated over the analgesic effect attained when each substance is considered separately, thereby achieving a synergistic effect approaching the analgesic effect of morphine.

Further objects and advantages will become apparent to one skilled in the art as the description of this invention proceeds.

The results of the acute tests, or experiments, are reflected in Tables 1 and 2 set out hereinafter in section "A". The chronic tests and experiments are described in section "B" hereinafter. The results of acute tests, or experiments, using a combination of substances is reflected in Table 3 of section "C" set out hereinafter.

D-phenylalanine in pure form, or as part of DL-phenylalanine, has been administered to 47 humans with both acute (4) and chronic (43) pain. Analgesia has been obtained in at least 28 (60%) of the subjects.

A. General Description Of Acute Tests
Of Individual Substances, And
Effect Of The Substances Tested

The tests herein described were intended to establish at least one safe and practical method of securing in animal species, such as mammals, a long lasting, or prolonged, analgesic effect from the enkephalins, and possibly of the endorphins, naturally occurring in the animal.

One test for the ability of the animal to withstand pain is the hot-plate test. It is a traditional pharmacological

screening procedure in which drug-treated mice are placed on a hot plate and the analgesic effect of the drug is measured by how soon a mouse jumps off the hot plate. In the specific hot-plate test described herein the temperature of the plate was maintained at 55°C.

Another test for the ability of the animal to withstand pain is the phenylquinone writhing test. Phenylquinone, when injected into mammals such as mice causes intense pain manifested by stretching, pelvic twisting, and extension of hind legs. An analgesic such as morphine, when administered to the mouse, will either abolish or reduce the number of such reactions to phenylquinone, the totality of response being known as writhing.

The practical method of administering the inhibitor or analgesic substances herein described in mice was by intraperitoneal injection. The dosage injected was 250 mg/kg, the dosage being proportional to the weight of the mouse treated.

The "control" for the hot-plate test is determined by placing an untreated mouse on a metal hot plate maintained at 55°C. The time it takes the untreated or "control" mouse to jump, after being placed on the hot plate, is noted. After being treated by an intraperitoneal injection, the mouse is again placed on the hot plate, and the lapse of time until the animal jumps is noted. This test of a treated mouse is repeated at various specified times. Specifically, the mouse is tested after a single injection for 2 hours at 30-minute intervals. In the experiments with mice, six to twelve mice were tested with each dose of injected substance.

A "highly significant" analgesic effect will be demonstrated by a time lapse, before the mouse jumps, constituting an increase of several-fold (3 or 4) over that of the control.

In the writhing test, the analgesic injected is administered to certain mice approximately one hour before injecting the phenylquinone. Other animals serving as a "control" are injected with saline solution approximately one hour before injecting the phenylquinone. The percent of animals writhing, together with the number of writhes is noted over a period of 10 minutes following injection of the phenylquinone.

The human studies noted herein were carried out on 47 subjects experiencing acute and chronic pain which had not been relieved by conventional treatment with drugs or other procedures such as acupuncture, transcutaneous nerve stimulation, or laminectomy. D-phenylalanine plus aspirin, D-phenylalanine alone, or DL-phenylalanine were administered orally and the degree of relief from pain was monitored for a period of several weeks.

The results of all tests were subjected to statistical analysis to determine the degree of significance of results.

Effect Of The Substances Tested

D-phenylalanine and hydrocinnamic acid both exhibited highly significant analgesia by the hot-plate test. This conclusion is supported by the data shown in Table 1. With injection of a saline solution, as a control, no

significant increase in jump time was observed or noted. With injection of D-phenylalanine or hydrocinnamic acid, a highly significant increase in time lapse before jump was observed.

5. Table 1 -- Analgesic Potency of Inhibitors of Enkephalin Breakdown, As Determined by the Hot Plate Method.

Treatment (Injection)	% Increase in Jumping Time
Saline	30%**
D-phenylalanine	300%*
10 L-phenylalanine	30%**
Hydrocinnamic acid	300%*

* Highly significant

** Not significant

Specificity of D-phenylalanine as an inhibitor substance is determined by comparison of results from its injection with results from injection of L-phenylalanine, a natural occurring amino acid, whose testing showed minimal, if any, significant analgesic potency. It is known that L-phenylalanine is a poor inhibitor of carboxypeptidase A. Naloxone exhibits the ability to reverse analgesia produced by D-phenylalanine. Since naloxone is a highly specific antagonist of morphine and the endorphins, this effect of naloxone supports the theory that D-phenylalanine may be producing analgesia by a mechanism involving the endorphins.

25 Table 2 shows that injection of D-phenylalanine also significantly decreased the number of test animals showing writhing. Reduction in intensity of writhing is shown by the reduction in number of writhes per minute. Table 2 again shows that injection of L-phenylalanine has
30 relatively little effect.

Table 2 -- Analgesic Potency of Inhibitors of Enkephalin Breakdown, As Determined by the Phenylquinone Writhing Test

5 Treatment (Injection)	% Writhing	Number of Writhes/ Minute
Saline	90%	5.4
D-phenylalanine	60%	2.5*
L-phenylalanine	80%	4.4**

* Highly significant

** Not significant

- 10 Results using D-leucine in the hot plate and writhing tests are shown in the following Table 3. Just as in the case of D-phenylalanine, analgesia by D-leucine was reversed by naloxone. Results are also shown for the combination of D-phenylalanine and D-leucine in these tests.
- 15 Such results show the potentiation of action by the combination of these amino acids.

Table 3 -- Analgesic Potency of D-Leucine and D-Leucine Plus D-Phenylalanine as Determined by the Hot Plate and Phenylquinone Writhing Tests

20 Treatment (Injection)	Hot Plate % Increase in Jumping Time	Writhing Test # of Writhes per Minute
Saline	-	5.6
D-leucine, 250 mg/kg	300*	3.0*
25 D-leucine, 125 mg/kg + D-phenylalanine, 125 mg/kg	300*	-
D-leucine, 250 mg/kg + D-phenylalanine, 250 mg/kg	-	1.0*

* Highly significant

B. Chronic Experiments

D-phenylalanine was injected intraperitoneally, twice daily for nine (9) days, into mice, in an amount per injection of .250 mg per kg weight of the mouse. All animals were tested by the hot-plate test on the ninth day for appearance of analgesia, both before the injection of the phenylalanine as well as afterwards. Two types of controls were also run. One control group of mice was injected with saline solution; the other group was injected with L-phenylalanine. Twenty animals were used for each of the three groups.

After administration of the second dose of phenylalanine on the ninth day, the animals that had been injected with D-phenylalanine were injected with naloxone, 20 mg/kg. Naloxone is an antagonist of morphine. The purpose of this latter test was to test for withdrawal symptoms, because with opiate-dependent animals, the amount of injected naloxone will produce severe withdrawal symptoms including diarrhea, large weight loss, and jumping.

The following results were observed in the mice that had been injected with D-phenylalanine for nine (9) days.

(a) Tolerance to the analgesic effects did not develop. In other words, the degree of analgesia in the D-phenylalanine injected mice, as measured by the hot-plate test, on the ninth day was essentially the same as that observed on the first day. If morphine, or other opiate substance, had been administered in a similar fashion, by the ninth day the administration of morphine, in the same

amount as administered on the first day would have had very little analgesic effect, the latter result being a reflection of tolerance.

(b) There seems to be a cumulative effect from the repeated injections, over an extended period of time, of D-phenylalanine (i.e., excellent analgesia to the hot-plate test was observed in the mice as long as 12 hours after the last dose had been injected.)

(c) The control group of mice injected with saline solution or with L-phenylalanine exhibited virtually no analgesia.

The following results were observed, after naloxone injection, in mice that had been injected with D-phenylalanine for nine (9) days:

(d) No sign of addiction was observed from administration of the naloxone test: (i.e. there was no diarrhea, weight loss, jumping, etc.)

(e) Naloxone only abolished the analgesia. (This was to have been expected if analgesia is indeed due to involvement of enkephalin and/or endorphin in the process.)

The foregoing results from several tests demonstrate the efficacy of using inhibitors of enkephalin breakdown as analgesics. The substances are effective, do not produce tolerance or dependence, and are extremely safe. Even at very high doses of DPA given over an extended period of time, no deaths or tissue pathology were observed in any of the experimental animals. On the basis of the animal experiments, it was anticipated that either D-phenylalanine, or some other equivalent, such as a more potent inhibitor of breakdown of enkephalins, would be extremely useful as an analgesic in man.

The degree of analgesia obtained with D-phenylalanine is not, initially, as intense as that secured by use of morphine and other narcotic analgesics. However, it is conceivable that more potent inhibitors of enkephalin and/or endorphin breakdown might prove to be at least equivalent, and perhaps even more effective, analgesics than D-phenylalanine.

It is considered that the analgesia produced by the combination of D-phenylalanine and D-leucine is equivalent to that obtained with fairly large doses of morphine (15 to 20 mg/kg).

C. Combinations Of Enkephalin Breakdown
Inhibitors With Antipyretic-Analgesic
(Aspirin-Type) Drugs

It has been discovered that the analgesia produced by enkephalin breakdown inhibitors, such as D-phenylalanine, can be greatly enhanced, or potentiated, by having an anti-inflammatory, antipyretic drug combined therewith. Such antipyretic, anti-inflammatory agents may include aspirin, indomethacin, diclofenac sodium, ibuprofen also known by trademark "Motrin", tolmetin sodium also known by trademark "Tolectin", naproxen also known by trademark "Naprosyn" and equivalents. Such antipyretic-analgesics are commonly referred to as aspirin-type drugs. Such drugs themselves are inhibitors of various enzymes, particularly prostaglandin synthetase. Significantly, the hot-plate test reflects that injection of indomethacin or diclofenac sodium at a dose which failed to provide a significant increase in jumping time of a mouse, when combined with D-phenylalanine provided an unusually highly

effective analgesia as is reflected in Table 4. Prior to the invention herein, it could not have been predicted that such a combination would provide such an unusual effect. In fact, the analgesia obtained by use of the combination of substances approached that analgesia obtained by one of the most potent known analgesics, morphine.

For combination experiments involving D-phenylalanine and the aspirin-like synthetase inhibitors, the following procedure was used: A series of mice were first administered either indomethacin or diclofenac sodium. At various times, the animals were tested by the hot-plate method. After one hour, D-phenylalanine was administered at a dose of 250 mg/kg and the animals were tested for analgesia for another two hours. The results are shown in Table 4. When D-phenylalanine was administered to mice which had previously been treated with a synthetase inhibitor, the effect of the combination was to increase the jumping time 1100 or 1200%, i.e., eleven or twelvefold. In some instances, the increase was at the maximum equivalent to that of morphine or other narcotic analgesics. It will be recalled from Table 1 above that the same dose of D-phenylalanine caused an increase in jumping time of only 300%, while as shown in Table 4 that of the synthetase inhibitors gave essentially no analgesia. Thus, the results from the combination of the two substances represent a true synergism, or example of drug potentiation.

Table 4 -- Analgesic Potency of Combinations of D-phenylalanine and Indomethacin or Diclofenac Sodium.

Treatment	% Increase in Jumping Time
D-phenylalanine, 250 mg/kg	300
5 Indomethacin, 20 mg/kg	0
Indomethacin, 20 mg/kg followed by D-phenylalanine, 250 mg/kg	1100
Diclofenac sodium 40 mg/kg	33
10 Diclofenac sodium 40 mg/kg followed by D-phenylalanine, 250 mg/kg	1200

Preliminary experiments in treatment of pain in human subjects using D-phenylalanine, D-phenylalanine plus aspirin, or DL-phenylalanine, by oral route shows that the efficacy of these substances as analgesics in man has been confirmed. As shown in Table 5 which lists representative results, long lasting pain relief can be achieved with any of the above chemicals given for 3 or 4 days. No side effects, tolerance, or signs of addiction were observed in any patient.

20 Preliminary success in experiments in treatment of pain in human subjects was also achieved by using D-leucine.

Table 5 -- D-Phenylalanine (DPA) Analgesia In Humans

CONDITION	DURATION	PRIOR TREATMENT	TIME ON DPA	RESULT
Whiplash	2 years	Empirin, Valium	3 days	Complete relief, 1 month
Osteoarthritis, fingers, thumbs of both hands	5 years	Empirin, aspirin	Maintained	Excellent relief; joint stiffness reduced
Rheumatoid arthritis (left knee), osteo- arthritis of hands	Several years	Empirin + codeine	1 week	Considerable relief
Low back pain, neck pain	Several years	90 acupuncture	3 days	Low back pain gone; walked one mile
Low back pain	Several years	Spinal fusion, percutaneous nerve stimulation	3 days	Much less pain
Low back pain	Several years	Laminectomies, Depomedrol, per- cutaneous nerve stimulation	3 days	Good to excellent relief
Fibrositis of muscle	*	Empirin	3 days	Pain gone, recurred after 2 days
Migraine headache	Several years	*	2 days	Good relief, may prevent recurrence
Cervical osteo- arthritis plus post-operative pain	*	*	2 days	Very little pain
Severe lower back pain	Several years (intermittent)	Empirin, Valium	3 days	Excellent relief

* means information not available

In the treatment of pain in human subjects, reported in Table 5, the dosage of D-phenylalanine administered was in the range of 800 - 1,000 mg. per day, administered in 4 equal installments of 200 - 250 mg. per dosage. These amounts had
5 been selected conservatively. When administration was with aspirin, 300 mg. aspirin was added to the D-phenylalanine.

When DL-phenylalanine was administered, the installments were of double weight, on the assumption that the D-phenylalanine component of the DL-phenylalanine was 50%.

10 The anticipated preferred range of administration of D-phenylalanine is 100 - 750 mg. dosage, taken four times per day, or a total of 400 - 3,000 mg. per day. When said preferred range of dosage is administered with aspirin, the aspirin component will be at a fixed rate of 300 mg. per
15 dosage.

For the preparation of pharmaceutical compositions, the active ingredients listed above can be brought into a suitable dosage form by conventional methods.

Merck Patent Gesellschaft
mit beschränkter Haftung
D a r m s t a d t

Patent Claims

1. Method of using at least one compound selected from the group consisting of D- and DL-phenylalanine, D- and DL-leucine and hydrocinnamic acid for the production of pharmaceutical preparations with analgetic activity.
2. Method of using D-phenylalanine in an amount of 100 to 750 mg. per dosage unit for the production of pharmaceutical preparations with analgetic activity.
3. Method of using D-phenylalanine in combination with D-leucine for the production of pharmaceutical preparations with analgetic activity.
4. Method of using at least one compound selected from the group consisting of D- and DL-phenylalanine, D- and DL-leucine and hydrocinnamic acid in combination with a prostaglandin synthetase inhibitor for the production of pharmaceutical preparations with analgetic activity.

5. Method of using inhibitors of the destruction of endogenous substances selected from the group including enkephalins and endorphins for effecting analgesia in animals.
6. Method of using at least one compound selected from the group consisting of D- and DL-phenylalanine, D- and DL-leucine and hydrocinnamic acid for effecting analgesia in animals.
7. Method according to any of Claims 5 or 6 comprising the additional use of a prostaglandin synthetase inhibitor.
8. Method according to Claim 7 comprising the additional use of at least one prostaglandin synthetase inhibitor selected from the group consisting of acetylsalicylic acid, indomethacin and diclofenac sodium.
9. Analgesic comprising an amount of 100 to 750 mg. of at least one compound selected from the group consisting of D- and DL-phenylalanine, D- and DL-leucine and hydrocinnamic acid per dosage unit.
10. Analgesic according to Claim 9 comprising additionally at least one prostaglandin synthetase inhibitor selected from the group consisting of acetylsalicylic acid, indomethacin and diclofenac sodium.



European Patent
Office

EUROPEAN SEARCH REPORT

0004040

Application number

EP 79 10 0614

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
	No relevant documents have been disclosed. -----		A 61 K 31/195 31/19 31/60 31/405// (A 61 K 31/195, 31/195)// (A 61 K 31/195, 31/19)// (A 61 K 31/60, 31/195)// (A 61 K 31/60, 31/19)// (A 61 K 31/405, 31/195)//
			TECHNICAL FIELDS SEARCHED (Int. Cl.)
			A 61 K 31/195 31/19 31/60 31/405
			CATEGORY OF CITED DOCUMENTS
			X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons
			&: member of the same patent family, corresponding document
b The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
The Hague	24-04-1979	BRINKMANN	

0004040'



EUROPEAN SEARCH REPORT

Application number

EP 79 10 0614

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. ⁷)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
			(A 61 K 31/405, 31/19)
			TECHNICAL FIELDS SEARCHED (Int. Cl. ⁷)

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record.**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☒ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER: _____**

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.